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(56) Documents cited
The Extra Pharmacopoeia Martindale 28th Ditn 1982 pages 1704–1705 The Theory and Practice of Industrial Pharmacy Lachman Lieberman & Kanig 2nd Editn Lea & Febiger pages 331 341–342 The Pharmaceutical Codex 11th Editn 1979 page 907 re "Effervescent tablets" page 727 re "Effervescent powders" and page 198

(58) Field of search
A5B

(54) Effervescent preparations containing diphosphonates

(57) Pharmaceutical formations for the administration of diphosphonates for treating impaired conditions of the phosphorus-calcium metabolism, having a better absorption degree comprise diphosphonates in excipients suitable to give effervescent solutions e.g. citric acid/sodium carbonate/sodium bicarbonate. The formulations may be powders, granules or tablets and the phosphonates are preferably sodium etidronate, dichloromethylene diphosphonate, and amino-hydroxy-propan-butan-, pentan, hexan-diphosphonate.

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SPECIFICATION

New pharmaceutical forms containing diphosphonates

The present invention refers to new pharmaceutical forms for the administration of diphosphonates.

The diphosphonates are a class of compounds recently introduced in therapeutic practice for treating and correcting impaired conditions of phosphorus-calcium metabolism.

Several papers have been published on the activity of diphosphonates (sodium ethidronate, dichloromethylene-diphosphonates and amino-hydroxy-propan-, butan-, pentan-, hexan-diphosphonate and the like) in the inhibition of bone reabsorption which is enhanced in an abnormal way in many bone diseases such as Paget's bone disease, bone tumors, bone metastasis induced by tumors, as well as in ostheoporosis or in hyperparathyroidism etc.

Recently some diphosphonates have been used in the treatment of metastatic osteolysis.

This new possibility of application derives from specific studies on the action of diphosphonates on the bone reabsorption in tumoral osteolysis, studies started in 1977 and subsequently applied to animals (Jung 1979) and, finally, to humans.

The use of diphosphonates as bone reabsorption inhibitors has however noticeable drawbacks, essentially connected with the absorption, which can be summarised as follows:

(a) low absorption degree for oral administration;

(b) inconstant absorption and changing in time and from patient to patient.

These difficulties of absorption involve therefore, in oral administration, the use of high dosages, with consequent difficulties in the formulation of capsules, tablets etc., containing very high amounts of active principle and with noticeable discomfort for patients subjected to continuous administrations of capsules and tablets inducing disturbing gastralgies.

It has been now surprisingly found that the diphosphonates, administered in the form of effervescent formulations, exhibit higher activity that that induced by equal concentrations of the product in the form of tablets.

This is probably due to an enhanced gastrointestinal absorption induced by the effervescent form, as appears from the presence, in the patients urine, of phosphate concentrations higher than those found after administration of diphosphonates as tablets.

It is therefore evident that it is possible to reduce dosages and administration frequency, by means of the effervescent formulations, allowing therefore an easy treatment which is well tolerated by patients.

The concentrations of the diphosphonates can differ according to the intended use and according to the intrinsic activity degree of the different diphosphonates and they will range from 5 to 3000 mg for monodose sachets and monodose effervescent tablets.

Th following non limitative examples further illustrate the compositions according to the inv ntion

EXAMPLE 1

Effervescent tablets		
Alkylidene-diphosphonic acids	mg	1000
anhydrous citric acid	mg	500
anhydrous sodium carbonate	mg	375
sodium bicarbonate (granular)	mg	525
natural orange flavour	mg	5
sodium benzoate	mg	95
Total	mg	2500

EXAMPLE 2

Effervescent granular		
Alkylidene-diphosphonic acid	mg	1000
anhydrous sodium carbonate	mg	150
sodium bicarbonate	mg	280
saccharose	mg	3888
sodium saccharinate	mg	20
anhydrous citric acid	mg	700
anhydrous orange flavour	mg	460
natural orange flavour	mg	2
Total	mg	6500

EXAMPLE 3

Monodose sachet		
Alkylidene-diphosphonic acid	mg	200
sodium carbonate	mg	30
sodium bicarbonate	mg	55
sodium saccharinate	mg	5
anhydrous citric acid	mg	140
anhydrous lemon flavour	mg	90
saccharose	mg	229
natural lemon juice	mg	1
Total	mg	750

CLAIMS

1. Pharmaceutical formulations, suitable for the treatment of bone diseases containing diphosphonates, intended to be administered by the oral route, which formulations are in form of monodose sachets or tablets containing diphosphonates in excipients suitable to give effervescent solutions.
2. Formulation according to claim 1 containing from 5 to 3000 mg of active principle.
3. Formulations according to claim 1 or 2 suitable for use in the treatment of tumoral osteolysis or hyperparathyroidism conditions.
4. A pharmaceutical formulation substantially as described in Example 1, 2 or 3.
5. For use in the treatment of bone diseases, pharmaceutical formulations according to any one of the preceding claims.

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